CLAIMS

1. A recombinant protein whose essential constituent polypeptide sequence comprises:

- a 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) of a *Plasmodium* type parasite other than *Plasmodium vivax* which is infectious in man, the C-terminal fragment remaining normally anchored to the surface of the surface of the parasite at the end of its penetration phase into human erythrocytes in the event of an infectious cycle;
- or that of a portion of that fragment which is also capable of inducing an immune response which can inhibit an *in vivo* parasitemia in a host infected with such parasite;
- or that of a peptide which is capable of inducing a cellular and/or humoral immunological response equivalent to that produced by said p19 fragment or said portion of that fragment; and

wherein said recombinant protein comprises conformational epitopes which are unstable in a reducing medium and which constitute the majority of the epitopes recognized by human antisera formed against the corresponding *Plasmodium*.

2. The recombinant protein of claim 1 which is not recognized by said human antisera when it is in the reduced form.

3. The recombinant protein of claim 2 which is substantially free of any form of a recombinant protein having the same sequence of amino acids, yet in which the conformational epitopes which are unstable in a reducing medium and which constitute the majority of the epitopes recognized by human antisera formed against the corresponding *Plasmodium* are not in a conformational form as defined by:

(a) the atomic coordinates as detailed in Annexes I, II or II, obtained by crystallography; and

(b) the NMR fingerprints as illustrated in Figures 12.0a to 12.2c.

4. The recombinant protein of claim 2 in which at least 20% contains an epitope in a conformational form as defined by the NMR fingerprints as illustrated in Figures 12.0a to 12.2c.

5. The recombinant protein of claim 2 ~~or claim 3~~ which is in a pure state.

6. The recombinant protein of claim 1, which is recognized by human antisera formed against the corresponding *Plasmodium* or against a homologous *Plasmodium* when it is in its non reduced state or in a reduced non irreversible state, but is not recognized or is only recognized to a slight extent by these same antisera when it is irreversibly reduced.

7. The recombinant protein of claim 5 which is defined by the crystallized form with the atomic coordinates as detailed in Annexes I, II or III, and the NMR fingerprints as illustrated in Figures 12.0a to 12.2c.

8. The recombinant protein of claim 5 which has a very high degree of purity as determined by electrospray mass spectrometry.

9. The recombinant protein of claim 5 which elicits a long term memory response directed in a substantially specific manner against said conformational epitopes in animals to which they are administered.

10. The protein of claim 1 which inhibits the reactivity of an immune antiserum against p42 produced from the same MSP-1 protein and is itself only partially inhibited by an immune antiserum produced against p42.

11. The recombinant protein of claim 1 which is essentially free of any polypeptide having a sequence of amino acids in the C-terminal region of p33 (33 kDa N-terminal fragment) resulting from th natural cleavage of the p42 protein of the same MSP1 protein.

12. The recombinant protein of claim 1 which comprises, upstream of the polypeptide sequence of p19, a polypeptide region whose sequence is the C-terminal region of p33 resulting from the cleavage of p42 of the same MSP-1 protein, wherein said polypeptide region contains less than 50 amino acid residues.

13. The recombinant protein of claim 11 wherein said polypeptide region contains less than 10 amino acid residues.

14. The recombinant protein of claim 1 which comprises, upstream of the polypeptide sequence of p19, a polypeptide region whose sequence is the C-terminal region of the p33 resulting from the cleavage of p42 of the same MSP-1 protein, wherein said C-terminal portion is restricted to that part which is substantially conserved in *P. falciparum* and *P. vivax*.

15. The recombinant protein of claim 1 wherein the sequence of amino acids of said essential constituent polypeptide encompasses the sequences of the two EGF regions of the p19 protein.

16. The recombinant protein of claim 2 wherein the sequence of amino acids of said essential constituent polypeptide encompasses the two sequences of the two EGF regions of the p19 protein.

17. The recombinant protein of claim 3 wherein the sequence of amino acids of said essential constituent polypeptide encompasses the two sequences of the two EGF regions of the p19 protein.

18. The recombinant protein of claim 4 wherein the sequence of amino acids of said essential constituent polypeptide encompasses the two sequences of the two EGF regions of the p19 protein.

19. The recombinant protein of claim 5 wherein the sequence of amino acids of said essential constituent polypeptide encompasses the two sequences of the two EGF regions of the p19 protein.

20. The recombinant protein of claim 6 wherein the sequence of amino acids of said essential constituent polypeptide encompasses the two sequences of the two EGF regions of the p19 protein.

21. The recombinant protein of claim 7 wherein the sequence of amino acids of said essential constituent polypeptide encompasses the two sequences of the two EGF regions of the p19 protein.

22. The recombinant protein of claim 8 wherein the sequence of amino acids of said essential constituent polypeptide encompasses the two sequences of the two EGF regions of the p19 protein.

23. The recombinant protein of claim 9 wherein the sequence of amino acids of said essential constituent polypeptide encompasses the two sequences of the two EGF regions of the p19 protein.

24. The recombinant protein according to claim 1, wherein the constituent polypeptide carries a glycosylphosphatidylinositol (GPI) group of the type which enables the p19 fragment to anchor to the membrane of a eukaryotic cell infected with the MSP-1 protein.

25. The recombinant protein of claim 1, wherein the constituent polypeptide is free of the sequence of amino acids in the hydrophobic C-terminal portion of the p19 which intervenes in the induction of an anchoring of said p19 to the cell membrane of a host infected with a *Plasmodium* type parasite.

26. The recombinant protein according to claim 24, which is hydrosoluble.

27. The recombinant protein of claim 1 which comprises the sequences of amino acids of the p19 of the MSP-1 protein of *Plasmodium falciparum*.

28. The recombinant protein of claim 1 which comprises the sequence of amino acids of the MSP-1 protein of *Plasmodium cynomolgi*.

29. An oligomer comprising the recombinant protein of claim 1.

30. The oligomer of claim 29, which comprises from 2 to 50 monomer units of the sequence of said recombinant protein.

31. The recombinant protein of claim 1, which is conjugated to a carrier molecule for use in the production of vaccines.

32. A vaccination composition against a *Plasmodium* type parasite which is infectious in man, containing as an active principle a recombinant protein whose essential constituent polypeptide sequence comprises:

- a 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) of a *Plasmodium* type parasite which is infectious in man, said C-terminal fragment remaining normally anchored to the surface of the parasite at the end of its penetration phase into human erythrocytes in the event of an infectious cycle;
- or that of a portion of that fragment which is also capable of inducing an immune response which can inhibit an *in vivo* parasitemia in a host infected with such parasite;
- or that of a peptide which is capable of inducing a cellular and/or humoral immunological response equivalent to that produced by said p19 fragment or said portion of that fragment; and

said recombinant protein further comprising conformational epitopes which are unstable in a reducing medium and which constitute the majority of the epitopes recognized by human antisera formed against the corresponding *Plasmodium*.

33. The vaccinating composition of claim 32, wherein said recombinant protein is not recognized by said human antisera when it is in the reduced form.

34. The vaccinating composition of claim 32, wherein said recombinant protein is substantially free of any form of said recombinant protein

having the same sequence of amino acids, yet in which the conformational epitopes which are unstable in a reducing medium and which constitute the majority of the epitopes recognized by human antisera formed against the corresponding *Plasmodium* are not in the conformational form as defined by:

(a) the atomic coordinates as detailed in Annexes I, II or II, obtained by crystallography; and

(b) the NMR fingerprints as illustrated in Figures 12.0a to 12.2c.

35. The vaccinating composition of claim 32, wherein said recombinant protein is in a pure state.

36. The vaccinating composition of claim 32, wherein said recombinant protein is recognized by human antisera formed against the corresponding *Plasmodium* or against a homologous *Plasmodium* when it is in its non reduced state or in a reduced non irreversible state, but is not recognized or is only recognized to a slight extent by these same antiserums when it is irreversibly reduced.

37. The vaccinating composition of claim 32, wherein said recombinant protein is defined by the crystallized form with the atomic coordinates as detailed in Annexes I, II or III, and the NMR fingerprints as illustrated in Figures 12.0a to 12.2c.

38. The ~~vaccinating~~ vaccination composition of claim 32, wherein said recombinant protein has a very high degree of purity as determined by electrospray mass spectroscopy.

39. The ~~vaccinating~~ vaccination composition of claim 32, wherein said recombinant protein elicits a long term memory response directed in a substantially specific manner against said conformational epitopes in animals to which th y are administered.

40. The ~~vaccinating~~ vaccination composition of claim 32, wherein the sequence of amino acids of said essential constituent polypeptide encompasses the sequences of the two EGF regions of the p19 protein.

41. The ~~vaccinating~~ vaccination composition of claim 33, wherein the sequence of amino acids of said essential constituent polypeptide encompasses the sequences of the two EGF regions of the p19 protein.

42. The ~~vaccinating~~ vaccination composition of claim 34, wherein the sequence of amino acids of said essential constituent polypeptide encompasses the sequences of the two EGF regions of the p19 protein.

43. The ~~vaccinating~~ vaccination composition of claim 35, wherein the sequence of amino acids of said essential constituent polypeptide encompasses the sequences of the two EGF regions of the p19 protein.

44. The ~~vaccinating~~ vaccination composition of claim 36, wherein the sequence of amino acids of said essential constituent polypeptide encompasses the sequences of the two EGF regions of the p19 protein.

45. The ~~vaccinating~~ vaccination composition of claim 37, wherein the sequence of amino acids of said essential constituent polypeptide encompasses the sequences of the two EGF regions of the p19 protein.

46. The ~~vaccinating~~ vaccination composition of claim 38, wherein the sequence of amino acids of said essential constituent polypeptide encompasses the sequences of the two EGF regions of the p19 protein.

47. The ~~vaccinating~~ vaccination composition of claim 32 wherein the essential constituent polypeptide of said recombinant protein comprises the sequence of the p19 *Plasmodium falciparum*.

48. The ~~vaccinating~~ vaccination composition of claim 32 wherein the essential constituent polypeptide of said recombinant protein comprises the sequence of the p19 *Plasmodium vivax*.

49. An antibody which specifically recognizing th p19 of a MSP-1 protein of the merozoite form of a *Plasmodium* type parasite which is

infectious in man other than *Plasmodium vivax* and which does not recognize *Plasmodium vivax*.

50. The antibody of claim 49, which is monoclonal.

51. The monoclonal antibody of claim 50, which specifically recognizes the p19 of *P. falciparum*.

52. The monoclonal antibody of claim 50, which specifically recognizes the p19 of *P. vivax*.

53. A recombinant baculovirus type modified vector containing, under the control of a promoter contained in the vector and able to be recognized by cells transfectable by said vector, a first nucleotide sequence coding for a signal peptide and a second nucleotide sequence downstream of the first nucleotide sequence, also under the control of said promoter, wherein said first nucleotide sequence authorizes the expression of said second nucleotide sequence in a baculovirus system and wherein said second nucleotide sequence codes for one of the following peptide sequences:

- a 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) of a *Plasmodium* type parasite which is infectious in man, the C-terminal fragment remaining normally anchored to the surface of the parasite at the end of its penetration phase into human erythrocytes in the event of an infectious cycle;
- or of a portion of that peptide fragment provided that the expression product from the second sequence in a baculovirus system is also capable of inducing an immune response which can inhibit an *in vivo* parasitemia in a host infected with said parasite;

- or of a peptide which is capable of inducing a cellular or humoral immunological response equivalent to that produced by said peptide fragment p19 or said peptide fragment portion; and

wherein said second nucleotide sequence has a G and C content in the range of from 40% to 60% of the totality of nucleotides from which said second nucleotide sequence is constituted.

54. The vector of claim 53, wherein said second nucleotide sequence has a G and C content in the range of at least 50% of the totality of nucleotides from which said second nucleotide sequence is constituted.

55. The vector of claim 53, wherein the second nucleotide sequence is a synthetic sequence.

56. The vector of claim 53, wherein the first nucleotide sequence codes for a signal peptide from *Plasmodium vivax* or *Plasmodium falciparum* normally associated with the *Plasmodium* MSP-1 protein.

57. The vector of claim 53, which consists of a modified baculovirus.

58. An organism transfected by the vector of claim 53.

59. A synthetic DNA containing a first nucleotide sequence including a portion which codes for the peptide sequence:

- of a 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) of *Plasmodium falciparum*, said C-terminal fragment remaining normally anchored to the surface of the parasite at the end of its penetration phase into human erythrocytes in the event of an infectious cycle;
- or of a portion of that peptide fragment provided that the expression product of said DNA in a baculovirus system is also capable of inducing an immune response which can inhibit an *in vivo* parasit mia in a host infected with such parasite;

- or of a peptide capable of inducing a cellular or humoral type immunological response equivalent to that produced by said p19 peptide fragment or said portion of that fragment or both; and

wherein said nucleotide sequence has a G and C nucleotide content in the range of from 40% to 60% of the totality of nucleotides from which said synthetic DNA is constituted.

60. The synthetic DNA of claim 59, wherein said nucleotide sequence has a G and C content of at least 50% of the totality of nucleotides from which said synthetic DNA is constituted.

61. The synthetic DNA sequence of claim 59, which further comprises upstream from said first nucleotide sequence, a second nucleotide sequence coding for a signal peptide normally associated with a *Plasmodium* MSP-1 protein which is homologous or heterologous relative to said first nucleotide sequence.

62. The synthetic DNA sequence of claim 61, wherein the signal sequence originates from *P. vivax*.

63. A baculovirus type selected from the group comprising:

- a virus deposited at the CNCM [Collection Nationale de Cultures de Microorganismes; National Collection of Microorganism Cultures] with registration number I-1659;
- a virus deposited at the CNCM with registration number I-1660;
- a virus deposited at the CNCM with registration number I-1661;
- a virus deposited at the CNCM with registration number I-1662;
- a virus deposited at the CNCM with registration number I-1663; and
- a virus deposited at the CNCM with registration number I-2041.

64. A hybridoma secreting the monoclonal antibodies of claim 50.

65. A hybridoma secreting the monoclonal antibodies of claim 51.

66. A hybridoma which secretes the monoclonal antibody of claim 50, which has been deposited at the CNCM, (Paris, France) with registration number I-1846, on the 14th of February 1997.

67. A ~~vaccine~~ Vaccination composition according to claim 32, which comprises a mixture of nucleotide sequences selected from the mixtures of recombinant proteins comprising the sequences of:

- *P. falciparum* p19 and *P. vivax* p19;
- *P. falciparum* p19 and *P. falciparum* p42;
- *P. vivax* p19 and *P. vivax* p42;
- *P. falciparum* p19 and *P. falciparum* p42; and *P. vivax* p19 and *P. vivax* p42.

Add C4

Add D1

Add E13